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(54) Title: CATALYST FOR ASYMMETRIC (TRANSFER) HYDROGENATION

WO 02/04466 (57) Abstract: Catalyst for the asymmetric (transfer) hydrogenation represented by the formula $ML_aX_bS_c$, where M is a transition metal, to be chosen from rhodium and ruthenium, and X is a counter ion and S is a ligand, a ranges from 0.5 to 3 and b and c, each independently, range from 0 to 2, and L is a chiral ligand having the formula (1), where C_n together with the two 2 O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms, R¹ and R² each independently represent H, an optionally substituted alkyl, aryl, alkaryl or aralkyl group or may form a (heterocyclic) ring together with the N-atom to which they are bound. And a process for the asymmetric (transfer) hydrogenation of an olefinically unsaturated compound, ketone, imine or oxime derivative in the presence of a hydrogen donor and of a catalyst, use being made of a catalyst represented by formula $ML_aX_bS_c$, where M is a transition metal, to be chosen from rhodium, iridium and ruthenium, X is a counter ion, S is a ligand, a ranges from 0.5 to 3 and b and c range from 0 to 2, and L is a chiral ligand having the formula (1), where C_n together with the two 2 O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms; and R¹ and R² are as defined above.

CATALYST FOR ASYMMETRIC (TRANSFER) HYDROGENATION

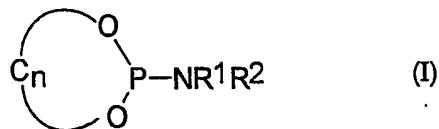
5 The invention relates to a catalyst for the asymmetric (transfer) hydrogenation that contains a transition metal compound and a chiral ligand.

Such catalysts are known from G. Franciò, F. Faraone and W. Leitner, *Angewandte Chemie. Int. Ed.* 2000, 39, 1428-1430. This publication describes the use of bidentate phosphine phosphorus amidite ligands for the 10 asymmetric hydrogenation of substituted olefins with enantioselectivities of up to 98.8%.

A drawback of the known catalysts is that the ligands used are generally prepared via many reaction steps, a number of which often proceed with a low yield. This makes these ligands extremely expensive. Another drawback of 15 these phosphine containing ligands is that they are relatively sensitive to oxygen, which causes problems in handling them in practice.

The invention now provides a catalyst consisting of a transition metal catalyst and a chiral ligand in which the ligand can simply be prepared in one or two steps from commercially available starting materials.

20 According to the invention this is achieved with a catalyst represented by the formula $ML_aX_bS_c$, where M is a transition metal, to be chosen from rhodium and ruthenium, L is an enantiomerically enriched chiral monodentate ligand having the formula (I),



25 where C_n together with the two O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms, R^1 and R^2 each independently stand for H, an optionally substituted alkyl, aryl, aralkyl or alkaryl group, or may form a (heterocyclic) ring together with the N-atom to which they are bound, X is a counter ion and S is a ligand, a ranges from 0.5 to 3, b and c each independently range from 0 to 2. Preferably R^1 and R^2 each independently represent an alkyl group, for instance an alkyl group with 1-6 C-atoms, in particular 1-3 C-atoms, most preferably C_1 and C_2 represent a methyl group. The alkyl, aryl, aralkyl and alkaryl groups preferably have 1-20 C-atoms and can optionally be substituted 30 with for instance one or more hydroxy, alkoxy, nitrile or carboxylic ester groups, 35

or halogens. R¹ and/or R² may be part of a polymeric backbone.

It has, surprisingly, been found that a high enantioselectivity can be achieved in the asymmetric hydrogenation or asymmetric transfer hydrogenation of olefins, ketones and imines when using the monodentate ligands

5 of formula (I), which can be prepared in a simple manner. This is all the more surprising since it is generally assumed that bidentate ligands are needed to achieve a high enantioselectivity. Another advantage of the catalysts according to the invention is that the reaction rate increases with increasing pressure, without the enantioselectivity decreasing. As a result, a lower amount of catalyst will

10 suffice or a faster reaction can be obtained. Yet another advantage is that the ligands according to the invention are virtually not sensitive to oxygen. Using a catalyst according to the invention in the asymmetric (transfer) hydrogenation of a prochiral compound, enantiomerically enriched compounds can be obtained with an ee of > 90%, in particular > 95%, more in particular > 98%.

15 The catalyst according to the invention represented by the formula ML_aX_bS_c may be neutral, anionic or cationic. The catalyst according to the invention may consist of a preformed complex having the formula ML_aX_bS_c. These complexes can be prepared by reacting the chiral ligand with a catalyst precursor. Preferably, however, the catalyst is formed *in situ* by adding the chiral ligand to a

20 solution of a catalyst precursor which may contain a ligand that is easily removed by hydrogenation. The amount of optically active ligand to be added for example may range from 0.5 to 5, preferably from 1 to 3.5, equivalents relative to the metal. Preferably a small excess of optically active ligand is applied relative to the desired amount of optically active ligand in the catalyst. The optimum ratio of

25 optically active ligand to metal in the catalyst may differ per optically active ligand and per metal and can readily be determined by means of experiments.

The catalyst can be activated by means of hydrogenation (prehydrogenation) prior to the addition of the substrate. It has been found that without this pretreatment of the catalysts according to the invention the same or

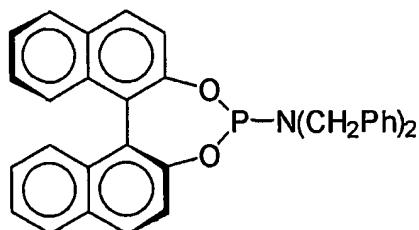
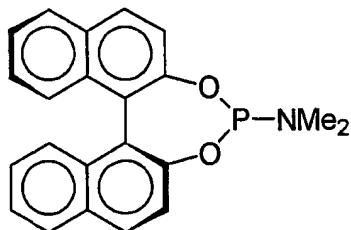
30 an even higher enantioselectivity is achieved.

Examples of suitable catalyst precursors are (COD = 1,5 cyclooctadiene; nbd = norbornadiene; L = ligand I; S = a ligand as defined below): [Rh(COD)₂Cl]₂, [Rh(COD)₂]BF₄, [Rh(nbd)₂]BF₄, [Rh(nbd)₂]ClO₄, [Ru(COD)Cl₂]_n, RhCl₃.nH₂O, Ru(OAc)₃, RuCl₃.nH₂O. Examples of preformed complexes are RhL₂(CH₃OH)₂BF₄, Rh(COD)L₂BF₄, RuL₂(OAc)₂, RuL₂Br₂, Ru(methylallyl)₂L₂, Ru(eta-6-benzene)L₂Br₂, Ru(eta-5-cyclopentadienyl)L₂Cl,

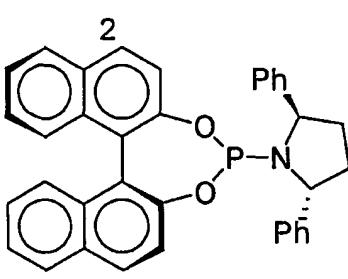
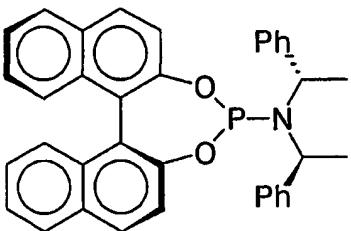
RuL₂Cl₂, RuLSCl₂, Ru (1,2-diphenyl-1,2-diaminoethane)LCl₂.

In the chiral ligand L of formula (I) C_n and/or R¹ and/or R² are chiral or are part of a chiral entity. C_n preferably represents a chiral substituted C₄ chain (chain with 4 optionally substituted C-atoms), of predominantly one 5 configuration, for example with an enantiomeric excess larger than 95%, in particular larger than 99%, more in particular larger than 99.5%. Preferably C_n together with the two O-atoms and the P-atom forms a 7-membered ring with 4 C-atoms which 2 by 2 form part of an aryl group or a naphthyl group. Examples of suitable chiral ligands according to the invention are

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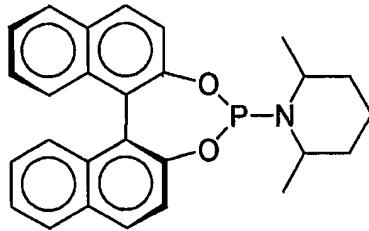
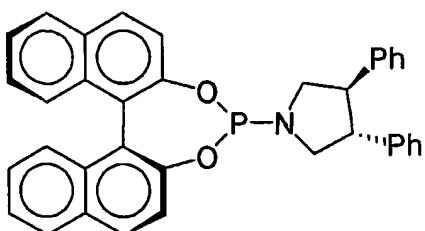


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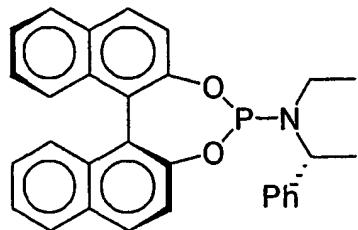
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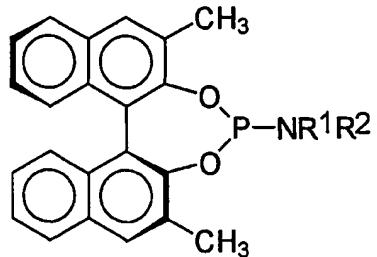
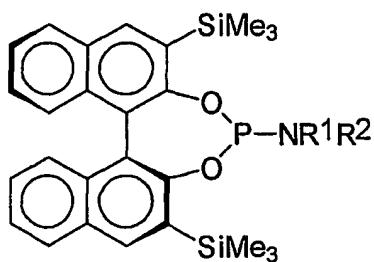
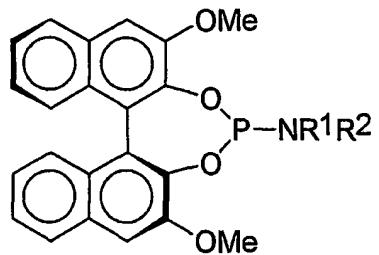
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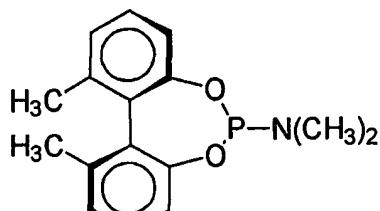
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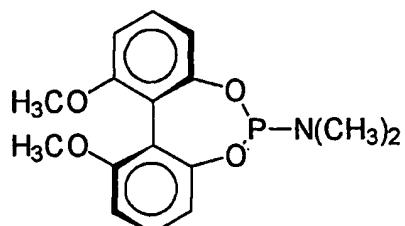


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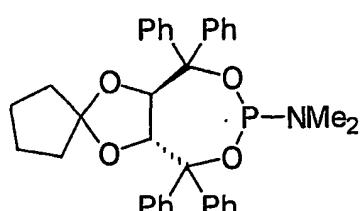
7 (R¹ and R² see text above)8 (R¹ and R² see text above)9 (R¹ and R² see text above)



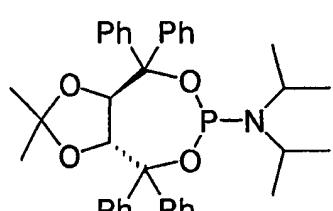
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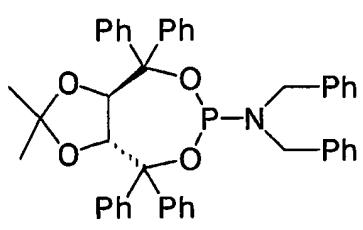
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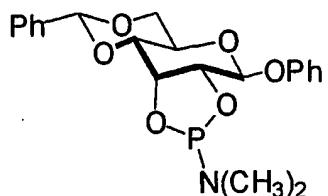
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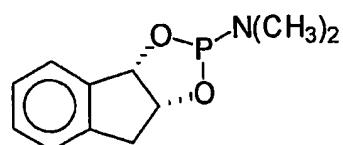
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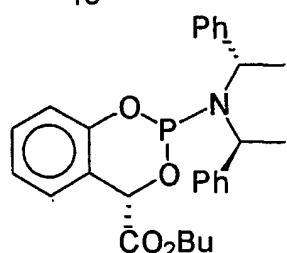
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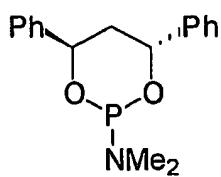
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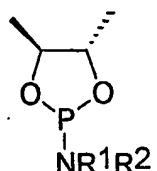
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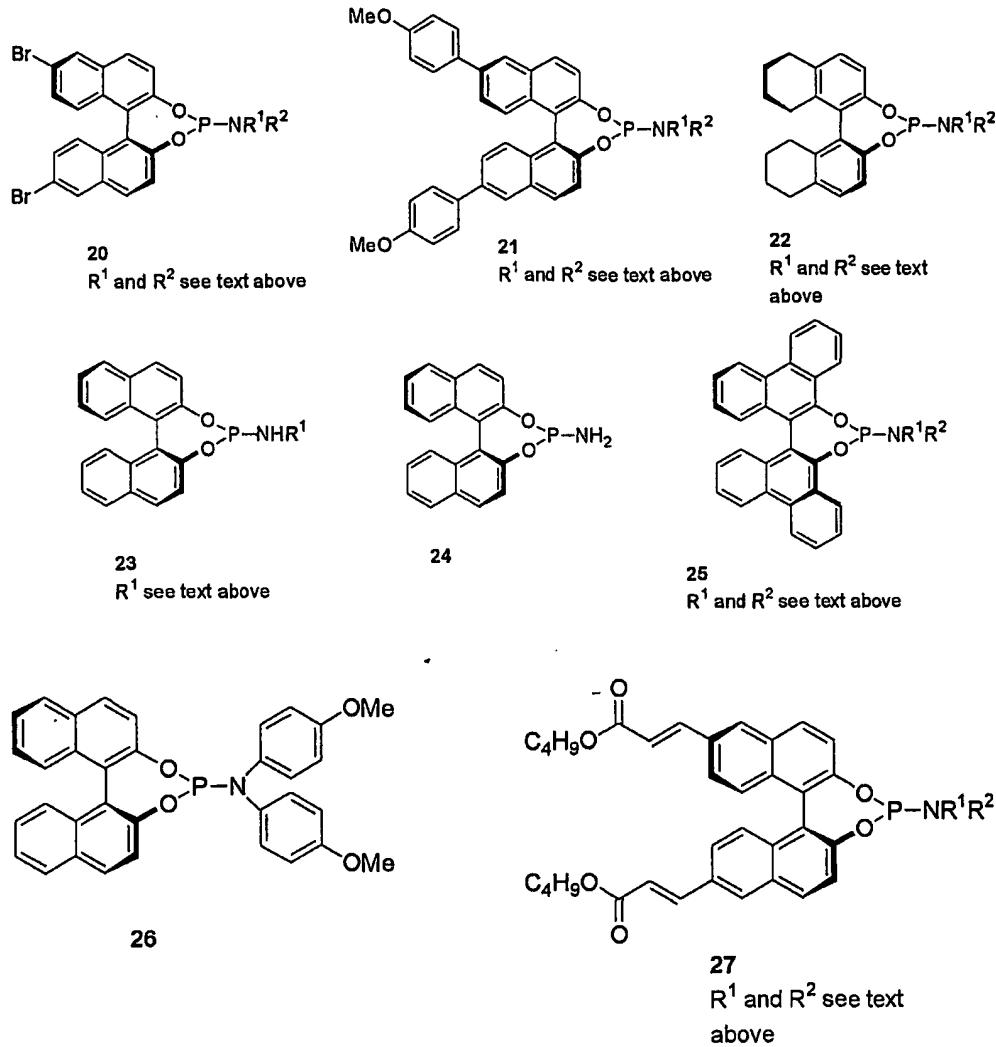
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19 (R1, R2 see text above)



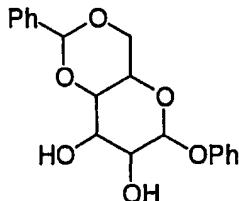
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It will be understood that where one enantiomer is represented, the other enantiomer is similarly applicable.

Such ligands with formula (I) can simply be prepared as described for example in *Houben-Weyl Methoden der Organischen Chemie Band XII/2. Organische phosphorverbindungen*. G. Thieme Verlag, Stuttgart, 1964, Teil 2 (4th ed.), pp. 99-105. A preferred preparation method is based on the reaction of an HO-C_n-OH compound with P(NMe₂)₃ or P(NEt₂)₃ (Me = methyl, Et = ethyl), with subsequent reaction with R¹R²NH, preferably in a solvent having a boiling point > 80 °C, for example toluene. Examples of suitable catalysts for the latter reaction are ammonium chloride, tetrazole or benzimidazoliumtriflate. Examples of HO-C_n-OH are chiral bisnaphthols for example (R)- or (S)- 1,1'-bi-

(2-naphthol), chiral bisphenols for example (R)- or (S)- 6,6'-dimethoxy-2,2'-bisphenol, diols, for example (R,R)- or (S,S)-2,2-dimethyl-1,3-dioxolane- 4,5-bis(1,1-diphenyl)methanol (TADDOL), or (S,R) or (R,S)-indane-1,2-diol; 1,2-diols and 1,3-diols based on sugars, for example diols having the formula:

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Examples of R^1R^2NH are benzyl amine, dibenzyl amine, diisopropyl amine, (R)- or (S)-1-methyl-benzyl amine, piperidine, morpholine, (R,R)- or (S,S)-bis-(1-methylbenzyl)amine.

A second preferred preparation is based on the reaction of an HO- C_n -OH compound with PCl_3 , with subsequent reaction with R^1R^2NH , preferably in the presence of a base, for example Et_3N , and in the presence of a solvent, for example toluene. Examples of HO- C_n -OH are in principle the same as mentioned above in relation to the first preferred preparation. Examples of R^1R^2NH are ammonia, benzyl amine, dibenzyl amine, diisopropyl amine, (R)- or (S)-1-methyl-benzyl amine, piperidine, morpholine, (R,R)- or (S,S)-bis-(1-methylbenzyl)amine.

If the catalyst of the invention with the formula $ML_aX_bS_c$ is cationic, then the counter ion X is an anion. Examples of suitable anions are Cl^- , Br^- , I^- , OAc^- , BF_4^- , PF_6^- , ClO_4^- , p-toluene sulphonate, benzene phosphonate, tetra-25 pentafluorophenylborate. Non-coordinating anions are preferred. If the catalyst is anionic, X is a cation. Examples of suitable cations are alkaline metals, for example Li, Na or K, alkaline earth metals such as Mg or Ca, or ammonium, or alkyl-substituted ammonium.

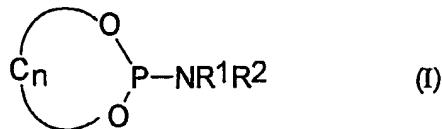
Ligand S may be chiral or non chiral. Suitable ligands S are 30 olefins, for example maleic anhydride or ethylene; dienes, for example 1,5-cyclooctadiene, 1,3-butadiene and 2,5-norbornadiene; aromatics, for example benzene, hexamethyl benzene, cymene and cumene, eta-5 coordinated cyclopentadienyl ligands, for example cyclopentadienyl and pentamethyl-35 cyclopentadienyl, diamines such as 1,2-diaminoethane. Examples of chiral ligands S are (R,R)-1,2-cyclohexanediamine, (S,S)-1,2-diphenyl-1,2-diaminoethane,

(S,S)-1,2-dicyclohexyl-1,2-diaminoethane or (S)-1,1' -bis(*p*-methoxyphenyl)-1,2-propanediamine.

The invention also relates to the preparation of the chiral ligands of formula I. In addition, the invention relates to the use of a catalyst represented

5 by the formula $ML_aX_bS_c$, where M is a transition metal, to be chosen from rhodium, iridium and ruthenium, and X is a counter ion and S is a ligand, a ranges from 0.5 to 3 and b and c, each independently, range from 0 to 2, wherein L is a chiral ligand of formula (I)

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where C_n together with the two O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms; and R^1 and R^2 are as defined above, in the asymmetric hydrogenation or in the asymmetric transfer hydrogenation of for

15 example olefins, ketones, imines and oxime derivates. C_n and/or R^1 and/or R^2 are chiral or are part of a chiral entity. Examples of suitable catalyst precursors, which together with the chiral ligand form the catalyst, are (COD = 1,5 cyclooctadiene; nbd = norbornadiene L = ligand I of the invention, S = a ligand as defined above):

[Rh (COD)Cl]₂, [Rh(COD)₂]BF₄, [Rh(nbd)₂]BF₄, [Rh(nbd)₂]ClO₄, [Ir(COD)Cl]₂,

20 [Ir(COD)₂]X (X = BF₄, PF₆, ClO₄, SbF₆, CF₃SO₃, B(C₆F₅)₄), [Ru(COD)Cl₂]_n.

Examples of preformed complexes are RhL₂(CH₃OH)₂BF₄, Rh(COD)L₂BF₄, RuL₂(OAc)₂, RuL₂Br₂, Ru(methylallyl)₂L₂, Ru(eta-6-benzene)L₂Br₂, Ru(eta-5-cyclopentadienyl)L₂Cl, RuLSCl₂, Ru(1,2-diphenyl-1,2-diaminoethane)LCl₂, IrL₂(CH₃OH)₂PF₆, Ir(COD)L₂BF₄.

25 In the preparation of the catalyst preferably a molar ratio of metal to the optically active ligand of between 2:1 and 1:10, preferably between 1:1 and 1:6, is chosen. Preferably the catalyst is prepared *in situ*, which means in the same pot as wherein the asymmetric (transfer) hydrogenation reaction is performed, without intermediate isolation of the catalyst.

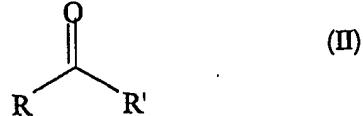
30 Suitable substrates for the asymmetric (transfer) hydrogenation are for example prochiral olefinically unsaturated compounds, in the context of this invention also referred to as olefins for short, in particular the alkylidene glycine derivatives, for example 2-acetylaminocinnamic acid, 2-benzoylaminocinnamic

acid, 2-acetylamino acrylic acid, N-acetyl-2-isopropylidene glycine, N-acetyl-2-cyclohexylidene glycine, N-acetyl-3'-methoxy-4-acetoxy-benzylidene glycine, 2-substituted maleic acids, for example 2-phenylmaleic acid, 2-methylmaleic acid; alkylidene-succinic acid derivatives, for example itaconic acid, 2-benzylidene-5-succinic acid, 2-isobutylidene-succinic acid; 1-substituted acrylic acid derivatives, for example 1-(6'-methoxy-naphthyl)-acrylic acid, 1-(4'-isobutylphenyl)acrylic acid, 1-substituted cinnamic acids, for example 1-methyl-cinnamic acid, 1-(hydroxymethyl)-cinnamic acid and 1-(chloromethyl)-cinnamic acid, and the salts of the above-mentioned compounds, for example the sodium, lithium, 10 tetraalkyl ammonium or trioctyl ammonium salts and the esters, for example the methyl, the ethyl and the *t*-butyl esters, of dicarboxylic acids also the mono-esters can be used.

Other suitable substrates are enamides for example 1-acetamidostyrene, (Z)-2-acetyl-1-(*p*-methoxybenzylidene)-N-acetyl-1-(3',4'-dimethoxy-benzylidene)-6,7-dimethoxy-1,2,3,4 tetrahydro-isoquinoline, 1-benzyloxycarbonyl-4-*t*-butoxycarbonyl-2,3-dehydro-piperazine-2-N-*t*-butylamide, enol ethers, for example 1-methoxy-styrene, enol esters, for example 5-methylidene-butyrolactone, allylic alcohols, for example 3,7-dimethyl-2,7-octadiene-1-ol (geraniol), nerol, 4-hydroxy-2-cyclopentenone. A recent survey of 20 the scope of asymmetric olefin hydrogenations is given, for example, by J.M. Brown in *Comprehensive Asymmetric Catalysis*, E.N. Jacobsen, A. Pfaltz and H. Yamamoto, eds. Springer, Berlin, 1999, Vol I, pp. 121-182.

Further suitable substrates are for example prochiral ketones having the general formula (II):

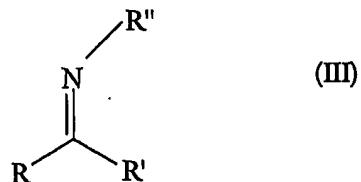
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where R and R' are not equal to one another and each independently from one another represent an alkyl group, aryl group, aralkyl group, alkenyl group or alkynyl group with 1-20 C-atoms or form a ring together with the C-atom to which they are bound, it being also possible for R and R' to contain one or more heteroatoms or functional groups, for example acetophenone, 1-acetonaphthone, 2-acetonaphthone, 3-quinuclidinone, 2-methoxycyclohexanone, 1-phenyl-2-

butanone, benzyl-isopropyl ketone, benzyl acetone, cyclohexyl methyl ketone, *t*-butylmethyl ketone, *t*-butylphenyl ketone, isopropyl phenyl ketone, ethyl-(2-methylethyl)-ketone, o-, m- or p-methoxyacetophenone, o-, m- or p-(fluoro, chloro, acetophenone, o-, m- or p-cyanoacetophenone, o-, m- and/or p-trifluoromethyl-
5 acetophenone, o-, m- or p-nitroacetophenone, 2-acetylfluorene, acetylferrocene, 2-acetylthiophene, 3-acetylthiophene, 2-acetylpyrrole, 3-acetylpyrrole, 2-acetylfuran, 3-acetylfuran, 1-indanone, 2-hydroxy-1-indanone, 1-tetralone, p-methoxyphenyl-p'-cyanophenylbenzophenone, cyclopropyl-(4-methoxyphenyl)-ketone, 2-acetylpyridine, 3-acetylpyridine, 4-acetylpyridine, acetylpyrazine, alpha-
10 haloketones, for example alpha-chloroacetophenone; alphaketo acids, for example pyruvic acid, phenylglyoxylic acid, 4-phenyl-2-oxo-butyric acid, 3-oxo, 4,4-dimethylbutyrolactone and esters and salts thereof; beta keto acids for example acetyl acetic acid, 4-phenylacetyl acetic acid, and esters and salts thereof; diketones, for example biacetyl, benzil, acetylacetone; hydroxyketones, for example
15 hydroxyacetone, benzoin and 1-phenyl-1hydroxyacetone.

Other prochiral compounds that can be used in the asymmetric (transfer) hydrogenation reaction are prochiral imines having the general formula (III):



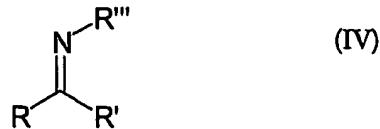
20 where R, R' and R'' for example each independently from one another represent an alkyl group, aryl group, aralkyl group, alkenyl group, or alkynyl group with 1-20 C-atoms or form a ring together with the atoms to which they are bound, it being also possible for R, R' and R'' to contain one or more heteroatoms and functional groups, and R'' furthermore may be a group that can be split off, for example a
25 phosphinyl, sulphonyl or benzyl group. Examples of imines are those prepared from the ketones described above and an alkyl amine or aryl amine or an amino acid derivative, for example an amino acid amide, an amino acid ester, a peptide or a polypeptide. Examples of a suitable alkyl amine or aryl amine are a benzyl amine, for example benzyl amine, or an o-, m- or p-substituted benzyl amine, an
30 α -alkyl benzyl amine, a naphthyl amine, for example naphthyl amine, a 1,2,3,4,5,6,7 or 8- substituted naphthyl amine, a 1-(1-naphthyl)alkyl amine or a 1-(2-naphthyl)alkyl amine or a benzhydryl amine. Examples of suitable imines are

N-(2-ethyl-6-methylphenyl)-1-methoxy-acetonimine, 5,6-difluoro-2-methyl-1,4-benzoxazine, 2-cyano-1-pyrroline, 2-ethyoxy carbonyl-1-pyrroline, 2-phenyl-1-pyrroline, 2-phenyl-3,4,5,6-tetrahydropyridine, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline, 1-(p-methoxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline,

5 N-diphenylphosphinyl 2-naphtophenone imine or N-tosyl-tetralone imine.

Other prochiral compounds that can be used in the asymmetric (transfer) hydrogenation reaction are prochiral oximes and derivatives thereof having the general formula (IV):

10



15

where R and R' are as defined above, R''' for example, represents an OH-group,

15

an ether group, an acyloxy group, a sulphonyloxy group. Examples of suitable oxime derivatives are acetophenone oxime, N-acetoxy-p-methoxyacetophenone-imine and O-methyl-p-chloroacetophenone oxime.

20

The catalysts according to the invention can also suitably be used in the preparation of an optically active compound, starting from a (racemic) mixture of the enantiomers of an) olefin, ketone, imine or oxime derivate that contains a chiral centre elsewhere in the molecule and with preferably one of the two enantiomers being hydrogenated.

25

The use of the catalysts according to the invention takes place in the presence of one or more hydrogen donors, which in the context of this

25

invention are understood to be compounds that can in some way transfer hydrogen to the substrate. Suitable hydrogen donors that can be used are preferably H₂, but may also be aliphatic or aromatic alcohols with 1-10 C-atoms, in particular secondary alcohols with 1-10 C-atoms, for example isopropanol or cyclohexanol, or unsaturated hydrocarbons with 5-10 C-atoms, for example

30

1,4 dihydrobenzene or hydroquinone, reducing sugars, for example glucose or derivates of formic acid, for example ammonium formate or an azeotropic mixture of formic acid and triethylamine.

35

The molar ratio of substrate to hydrogen donor preferably lies between 1:1 and 1:100. The hydrogen pressure may vary within wide limits and is preferably chosen to be as high as possible when a fast reaction or the lowest possible amount of catalyst is desired. The hydrogen pressure for example lies

between 0.05 and 20 MPa, preferably between 0.1 and 10 MPa, in particular between 0.15 and 8 MPa.

In the asymmetric hydrogenation use is preferably made of a molar ratio of metal present in the transition metal compound to substrate of

5 between 1:10 and 1:1,000,000, in particular between 1:50 and 1:100,000.

The catalyst may optionally be added in dimeric form, with the dimeric form subsequently wholly or partly changing *in situ* into the monomeric form.

The temperature at which the asymmetric (transfer)

10 hydrogenation is carried out is generally a compromise between reaction velocity and enantioselectivity, and preferably lies between -20 and 120°C, in particular between 0 and 60°C. The asymmetric (transfer) hydrogenation is preferably carried out with oxygen being excluded. Preferably the substrates and solvents do not contain any oxygen, peroxides or other oxidizing substances.

15 As solvent use can be made of: alcohols, esters, amides, ethers, ketones, aromatic hydrocarbons, halogenated hydrocarbons. Preferably use is made of ethyl acetate, 2-propanol, acetone, tetrahydrofuran (THF), dichloromethane, toluene or dibromoethane. It is also possible to carry out the asymmetric (transfer) hydrogenation in ionic liquids as described in T. Welton,

20 *Chem. Rev.*, 99, 2071-2083 (1999), so that isolation of the product is simplified. If necessary the solubility of the ligand in the ionic liquid can be increased by providing the ligand with polar groups such as carboxylate salts. If the substrate is a liquid, the hydrogenation can also very suitably be carried out without a solvent. If the substrate and/or the product hardly dissolves in the solvent the asymmetric

25 (transfer) hydrogenation can also be performed as a slurry. If the product forms a slurry, its isolation is very much simplified.

Preferably the (transfer) hydrogenation reaction is carried out without preceding prehydrogenation. However, it is also possible to activate the catalyst for the asymmetric (transfer) hydrogenation prior to the addition of the

30 substrate by hydrogenation with hydrogen or by treatment with a reducing agent, for example NaBH₄. The (transfer) hydrogenation reaction will sometimes also be accelerated by adding a base, an acid, a halide, or an N-hydroxyimide prior to or during the hydrogenation. Suitable bases are nitrogen bases for instance triethylamine, DBU, and substituted or non-substituted pyridines and mineral bases for example KOtBu or Cs₂CO₃. Suitable acids are for example HBr, trifluoroacetic

acid. Suitable halides are for example alkali halides or tetraalkylammonium halides e.g. LiI, LiBr, LiCl, NaI, tetrabutylammonium iodide. A suitable N-hydroxy-imide is for instance N-hydroxy-phtalic-imide.

The invention will be elucidated with reference to the following

5 examples, without however being restricted by these:

EXAMPLES

Example I

10 Synthesis of ligand 1

Under a slow nitrogen gas flow 7 mL (38 mmol) of hexamethylphosphorus triamide was added to a suspension of 10.0 g of S-(-)-1,1'-bi-2-naphthol (34.9 mmol) in 50 g of dry toluene at 40°C. After 1 minute the product started to crystallize. After 5 hours the solid was removed by filtration, 15 washed with toluene and pentane and dried. Yield: 11.0 g (30.6 mmol, 88%), pure product according to TLC (silica gel, EtOAc:hexane = 1:1, ^{31}P -NMR and ^1H -NMR).

Example II

Synthesis of ligand 2

20 A suspension of 0.36 g of ligand 1 (1.0 mmol), 0.07 g of tetrazole (0.9 mmol) and 0.394 mL of dibenzyl amine (2.0 mmol) in 4 mL of dry toluene was boiled for 5 hours with reflux under a slow nitrogen gas flow. Afterwards the solution was cooled and filtered over a thin layer of silica gel. After washing of the silica gel with 10% t-BuOMe in hexane the filtrate was thoroughly evaporated. 25 Yield: 0.44 g (0.87 mmol, 87%), pure according to ^{31}P -NMR and ^1H -NMR and TLC.

Example III

Synthesis of ligand 3

30 To a cooled solution (-60°C) of PCl_3 (3.0 mmol), Et_3N (6.0 mmol) and toluene (5 mL) was added a warm solution (60°C) of (S)-2,2-binaphthol (3.0 mmol) and toluene (25 mL) in 5 min. After stirring for 2 h the reaction mixture was warmed to room temperature and filtered under an argon atmosphere. The filtrate was treated with Et_3N (2.9 mmol) and 2.9 mmol of (*R,R*)-bis-(1-35 methylbenzyl)-amine at -40°C. After 16 h at ambient temperature, the reaction

mixture was filtered, concentrated and purified by chromatography. Yield: 41%, pure according to ^{31}P -NMR and ^1H -NMR and TLC.

Example IV: Hydrogenation of olefins

5 Method A. Hydrogenation at 0.1 MPa with prehydrogenation

Rh(COD)₂BF₄ (0.010 mmol) and chiral ligand (0.022 mmol) were weighed into a 10 ml Schlenk vessel, a magnetic stirring bar was added and the vessel was closed with a rubber septum. 3 Vacuum/nitrogen cycles were followed by 2 vacuum/hydrogen cycles. 1.5 mL of solvent is added and stirring under a hydrogen atmosphere of 0.1 MPa takes place for 1 hour. Subsequently a solution of substrate (0.2 mmol) in 3.5 mL solvent is added and the reaction mixture is stirred under a hydrogen atmosphere. Samples were filtered over silica gel with EtOAc : hexane 4:1 and evaporated. The e.e. was determined by chiral GC or HPLC, the conversion by ^1H -NMR. When the reaction was finished the reaction mixture was treated and evaporated, in the same way as the samples. Results are depicted in the Tables.

Method B. Hydrogenation experiment at 0.1 MPa (without prehydrogenation)

20 Rh(COD)₂BF₄ (0.010 mmol), chiral ligand (0.022 mmol) and substrate (0.2 mmol) were weighed into a Schlenk tube equipped with a rubber septum cap and a stirring bar. After three vacuum/nitrogen cycles 5 mL of freshly distilled solvent is added through the septum cap and the reaction mixture is stirred under a hydrogen atmosphere of 0.1 MPa. Samples and reaction mixture were treated as described in method A. Results are depicted in the Tables.

25

Method C. Hydrogenation at 0.5 MPa

30 Rh(COD)₂BF₄, chiral ligand (2.2. molequivalents in respect to Rh), and CH₂Cl₂ (10 mL) were added into a Schlenk vessel and stirred under a nitrogen atmosphere. The catalyst solution was transferred to a 50 mL Buchi miniclave by using a syringe. When solvents other than CH₂Cl₂ were applied in the hydrogenation, Rh(COD)₂BF₄ and chiral ligand were first dissolved in CH₂Cl₂ by stirring at RT under a nitrogen atmosphere for 10 minutes, CH₂Cl₂ was evaporated under vacuum, the desired solvent (10 mL) was added and subsequently this catalyst solution was transferred to the Buchi miniclave.

35

In a number of cases this solution was prehydrogenated for 1 hour under a hydrogen atmosphere of 0.1 MPa. The substrate (0.8 mmol)

dissolved in 10 mL solvent was added to the Buchi miniclave and a hydrogen pressure of 0.5 MPa was applied. Samples and reaction mixture were treated as described in method A. Results are depicted in the Tables.

5 Method D. Hydrogenation at 6 MPa

Rh(nbd)₂BF₄ (4.0 mg, 0.0099 mmol) and 8.6 mg of chiral ligand 1 (0.022 mmol) were dissolved under a nitrogen atmosphere in CH₂Cl₂ (2.5 mL, degassed) in a Schlenk tube equipped with a magnetic stirrer and septum cap. The orange solution was stirred for 5 minutes at room temperature, 10 and the solvent was removed by evaporation. The catalyst was dissolved in of EtOAc (20 mL, degassed). α -Acetamidocinnamic acid ester (240 mg, 1.09 mmol) was added to a 125 ml Parr autoclave. After three nitrogen pressure (0.29 MPa) – pressure release cycles EtOAc (30 ml) was added. The orange catalyst solution (20 ml) was added to the autoclave by using a syringe and a hydrogen pressure of 15 6.0 MPa was applied. The reaction mixture was stirred at 680 rpm using an overhead stirrer with a propeller stirring blade. Samples were taken after 4, 10 and 20 minutes. The reaction proved to be completed after 4 minutes. The conversion to N-acetyl-phenylalanine methyl ester was > 99% with an e.e. of 97%. See also Table 2.

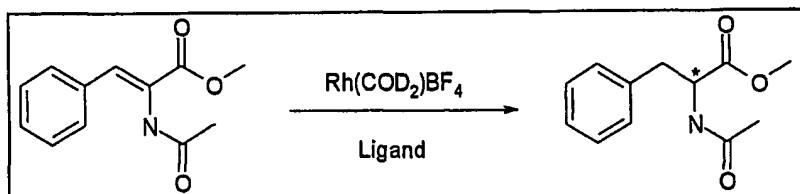
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Method E. Hydrogenation of different olefins and enamides at different Hydrogen pressures

Rh(COD)₂BF₄, chiral ligand (2.2 molequivalent to Rh), substrate, and solvent were weighed into an autoclave. The autoclave was closed and 25 inertised by three nitrogen pressure (0.29 MPa) – pressure release cycles. The desired hydrogen pressure was applied and the reaction mixture was stirred at 500 rpm using an overhead stirrer with a propeller stirring blade. The reactions were monitored by hydrogen uptake. Results are depicted in Table 6.

30

Table 1



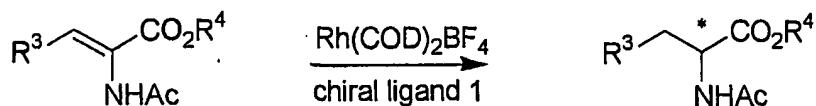
L	Lig. Conf.	Method	Temp. °C	Solvent	Time (min)	Conv. (%)	E.e. (%)	Prod. Conf.
1	S	A	RT	MeOH	1080	60	72	R
1	R	A	RT	MeOH	1320	98	75	S
1	R	A	RT	CH_2Cl_2	240	100	94.7	S
1	S	A	RT	CH_2Cl_2	240	100	95.5	R
1	S	A	RT	EtOAc	120	>98	91.2	R
1	S	A	5	CH_2Cl_2	180	96	97.2	R
1	S	A	-10	CH_2Cl_2	1080	86	98.0	R
1	S	A	-10	CH_2Cl_2	1080	92	97.9	R
1	S	A	RT	$\text{ClCH}_2\text{CH}_2\text{Cl}$	120	>98	88.9	R
1	S	A	RT	Acetone	270	92	92.4	R
1	S	A	RT	THF	270	75	93.6	R
1	S	B	RT	$\text{ClCH}_2\text{CH}_2\text{Cl}$	300	100	96.0	R
1	S	B	RT	CH_2Cl_2	120	94	97.0	R
1	S	B	RT	EtOAc	300	>98	95.6	R
				CH_2Cl_2 + 50 mL H_2O				
1	S	A	RT	H_2O	240	100	92.2	R
1	S	B	0	CH_2Cl_2	1200	100	97.6	R
1	S	B	0	EtOAc	1200	85	98.4	R
1	S	B	0	$\text{ClCH}_2\text{CH}_2\text{Cl}$	1200	100	97.6	R
1	S	B	-10	CH_2Cl_2	1200	64	97.9	R
2	S	A	RT	MeOH	1260	16	56	R
3	S,R,R	A	RT	CH_2Cl_2	240	100	42	R
6	S	A	RT	MeOH	11520	72	34	R
13	R,R	A	RT	MeOH	240	100	37	R
14	R,R	A	RT	MeOH	1440	100	77	S

Table 2 Hydrogenation of 2-acetamido-cinnamic acid methyl ester with chiral ligand 1 at elevated pressure (see Example IV)

Method	Prehydrogenation	Temp. (°C)	Solvent	Amount of Rh (mol%)	Time (min)	Conversion (%)	E.e. (%)
C	Yes	RT	CH ₂ Cl ₂	5	10	> 98	94.6
C	Yes	-5	CH ₂ Cl ₂	5	60	> 98	97.2
C	Yes	RT	CH ₂ Cl ₂	0.5	40	> 98	94.7
C	No	RT	CH ₂ Cl ₂	0.5	60	87	95.5
C	No	RT	Acetone	0.5	60	94	95.5
C	Yes	RT	EtOAc	0.5	60	58	95.7
C	No	RT	THF	5	30	> 98	95.9
D	No	RT	EtOAc	0.9	4	> 98	97

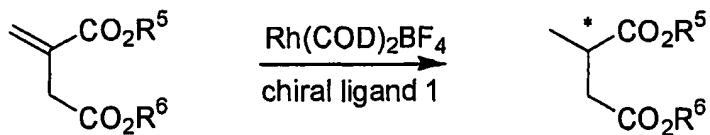
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Table 4 Hydrogenations of various olefins using the catalyst of the invention (see Example IV, method B, Conv. > 99%).



R ³	R ⁴	Temp (°C)	Solvent	Time (min)	E.e. (%)
H	Me	0	EtOAc	1200	>99
Ph	H	RT	EtOAc	1200	80
H	Me	RT	CH ₂ Cl ₂	240	>99
H	Me	RT	EtOAc	960	>99
H	H	RT	EtOAc	180	99
(p-OAc, m-OMe)-Ph	Me	RT	EtOAc	1200	94
(p-OAc, m-OMe)-Ph	Me	RT	CH ₂ Cl ₂	1200	95
(p-OAc, m-OMe)-Ph	Me	0	EtOAc	1200	98
(p-OAc, m-OMe)-Ph	Me	0	CH ₂ Cl ₂	1200	96
(p-F)-Ph	H	RT	EtOAc	270	76
(p-F)-Ph	Me	RT	CH ₂ Cl ₂	150	95

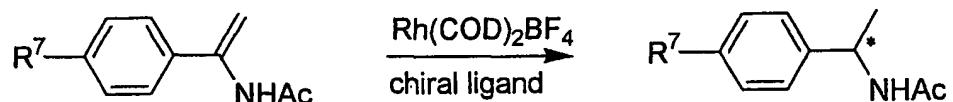
Table 5 Hydrogenations of itaconic acid and derivatives using the catalyst of the invention (see Example IV, at RT).



5

R ⁵	R ⁶	Method	Solvent	Time (min.)	Conv. (%)	E.e. (%)
Me	Me	A	CH ₂ Cl ₂	780	>99	87
H	H	B	EtOAc	1200	>99	97
Me	Me	B	CH ₂ Cl ₂	1200	>99	94
H	H	B	CH ₂ Cl ₂	1200	>99	95
Me	Me	C, No prehydrog., 0.5 mol% Rh	CH ₂ Cl ₂	60	75	91

Table 6 Hydrogenations of enamides using the catalyst of the invention (see Example IV, in CH_2Cl_2 , at RT, conv. > 99%).



5

R⁷	Ligand	Method	Amount of Rh (mol%)	Hydrogen Pressure (MPa)	Time (min.)	E.e. (%)
H	1	B	5	0.5	1200	92
<i>p</i> -Cl	2	E	2	1.5	210	58
<i>p</i> -Cl	20, R ¹ and R ² = Me	E	2	1.5	210	89
<i>p</i> -Cl	22, R ¹ and R ² = Me	E	2	1.5	210	86
<i>p</i> -Cl	1	E	2	1.5	210	93
<i>p</i> -Ome	1	E	2	1.5	240	84
<i>p</i> -Ome	22, R ¹ and R ² = Me	E	2	1.5	240	62
<i>p</i> -Ome	20, R ¹ and R ² = Me	E	2	1.5	240	83
<i>p</i> -Ome	2	E	2	1.5	240	53

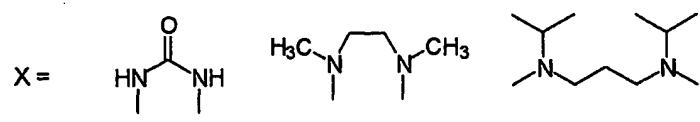
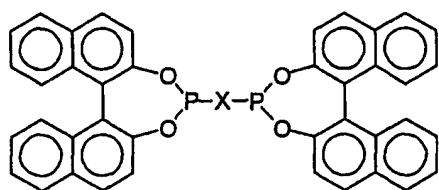
Comparative Experiment

Hydrogenation with chiral bidentate ligands (not forming part of 10 the invention). Hydrogenation of 2-acetamidocinnamic acid methyl ester according to method A (See Example IV), with 1.1 molequivalent of chiral ligand, unless stated otherwise). The results are given in Table 3. The results show that bidentate phosphoramido ligands generally lead to slow reactions with low enantioselectivity.

15

Table 3

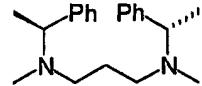
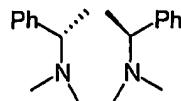
L	Lig. Conf.	Remarks	Solvent	Time (min.)	Conv. (%)	E.e. (%)	Prod. Conf.
28	S,S		MeOH	1140	100	22	R
28	S,S		CH ₂ Cl ₂	1140	100	42	R
29	R,R		MeOH	1380	6	52	R
29	R,R	2.2 eq. ligand	MeOH	1320	-	-	-
29	R,R		CH ₂ Cl ₂	1440	56	72	R
30	S,S		MeOH	1380	-	-	-
30	S,S	2.2 eq. ligand	MeOH	1320	-	-	-
30	S,S		CH ₂ Cl ₂	1440	100	25	S
31	R,S,R,S		MeOH	1260	18	12	S
31	R,S,R,S		CH ₂ Cl ₂	1440	7	28	R
32	S,S,S,S		MeOH	1260	40	6	R
32	S,S,S,S		CH ₂ Cl ₂	1440	100	80	S
33	R,R,R,R		MeOH	1320	100	14	S
34	R,R,R,R		MeOH	1320	40	15	S

Bidentate ligands, not forming part of the invention

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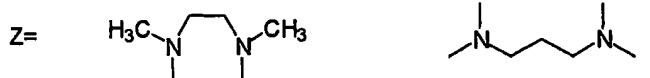
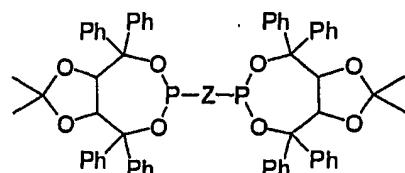
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Example V; Hydrogenation of acetophenoneSynthesis of the catalyst complex Ru(ligand)(diamine)Cl₂

[RuCl₂(*p*-cymene)]₂ (9 mg) and 2 equiv. of the ligand 1 (21.9 mg) were put in a schlenk-flask under N₂-atmosphere. DMF (1.0 ml) was added and

5 the mixture was degassed by 3 vacuum/N₂ cycles. Then it was stirred at 65 °C for 16–24 h (or 3 h 90 °C). A RuCl₂(ligand)₂(dmf)_n complex is formed. Then it is cooled to r.t. and 1 equiv. of (S,S)-1,2-diphenyl-1,2-diaminoethane (DPEN) (6.3 mg) was added. After stirring the mixture for another 16–24 h it was used for hydrogenation.

10 Spectroscopic data: RuCl₂(ligand)₂(dmf)_n P-NMR: 148.8 ppm; Ru(ligand)(DPEN)Cl₂ P-NMR: 147.7 (free ligand) and 172.2 (complex) ppm.

Preformed complex of formula Ru(L)Cl₂[(S,S)-1,2-diphenylethylenediamine] (0.1 mmol), and substrate (10 mmol), were weighed into an autoclave. Under a slow nitrogen flow degassed MeOH (50 mL) and K₂CO₃ (2.0 mmol) were added and the autoclave was closed and inertised by three nitrogen pressure (0.29 MPa) – pressure release cycles. The desired hydrogen pressure (5.0 MPa) and temperature (50°C) were applied and the reaction mixture was stirred at 500 rpm using an overhead stirrer with a propeller stirring blade.

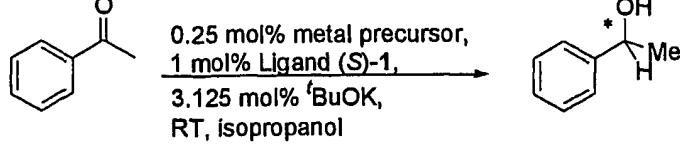
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20 Results:

L = Ligand 1: after 45 min, 93% conversion, with 58% e.e.

L = Ligand 1 wherein the N-methyl groups are replaced by i-propyl groups: after 150 min, 98% conversion, with 67% e.e.

25 Example VI Asymmetric transfer hydrogenation using ruthenium(II) and iridium(I) complexes of Ligand 1



30

Asymmetric reduction of acetophenone using an iridium(I) catalyst

A mixture of [IrCl(cod)]₂ (0.01 mmol, 0.25 mol%, 6.7 mg) and (S)-1 as a ligand (0.04 mmol, 1 mol%, 14.4 mg) in dry, degassed isopropanol

(5 ml) was heated at 80 °C for 1 h under nitrogen. After cooling to room temperature, the catalyst solution was added to a solution of potassium *tert*-butoxide (0.125 mmol, 3.125 mol%, 14.0 mg) and acetophenone (4 mmol, 471 µl) in dry, degassed isopropanol (35 ml). The reaction was stirred at room

5 temperature under nitrogen for the time indicated and monitored by GC analysis. Results are given in Table 7.

Asymmetric reduction of acetophenone using a ruthenium(II) catalyst

A mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.0125 mmol, 0.25 mol%, 7.7 mg) and (S)-Monophos as a ligand (0.05 mmol, 1 mol%, 18.0 mg) in dry, degassed isopropanol (5 ml) was heated at 80 °C for 1 h under nitrogen. After cooling to room temperature, the catalyst solution was added to a solution of potassium *tert*-butoxide (0.15 mmol, 3 mol%, 16.8 mg) and acetophenone (5 mmol, 588 µl) in dry, degassed isopropanol (40 ml). The reaction was stirred at

10 room temperature under nitrogen for the time indicated and monitored by GC analysis.

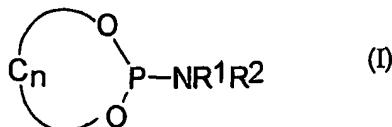
15 Results are given in Table 7.

20 **Table 7** Asymmetric transfer hydrogenation of acetophenone with isopropanol catalysed by ruthenium and iridium complexes.

Metal precursor	Time (h)	Conversion (%)	ee (major enantiomer)
$[\text{IrCl}(\text{cod})]_2$	1.5	8	25 (R)
	21	51	27 (R)
$[\text{RuCl}_2(p\text{-cymene})]_2$	1	17	47 (R)
	21	24	46 (R)

CLAIMS

1. Catalyst for the asymmetric (transfer) hydrogenation represented by the formula $ML_aX_bS_c$, where M is a transition metal, to be chosen from 5 rhodium and ruthenium, X is a counter ion and S is a ligand, a ranges from 0.5 to 3 and b and c, each independently, range from 0 to 2, characterized in that L is a chiral ligand having the formula



10 (I), where C_n together with the two O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms, R^1 and R^2 each independently stand for H, an optionally substituted alkyl, aryl, alkaryl or aralkyl group or may form a heterocyclic ring together with the N-atom to which they are bound.

15 2. Catalyst according to claim 1, where C_n represents a chiral substituted C4 chain that substantially has one particular configuration.

3. Catalyst according to claim 2, where C_n together with the two O-atoms and the P-atom forms a 7-membered ring with 4 C-atoms which two by 20 two form part of an aryl group or a naphthyl group.

4. Catalyst according to any one of claims 1-3 wherein R^1 and R^2 each independently represent an alkyl group.

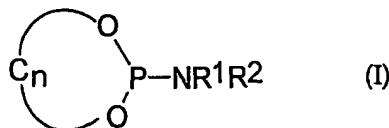
5. Catalyst according to claim 4 wherein R^1 and R^2 both represent a methyl group.

25 6. Process for the preparation of a ligand of formula 1, in which a diol, having the formula $HO-C_n-OH$ with n as defined above, is reacted with $P(N(R^3)_2)_3$ wherein R^3 is methyl or ethyl, followed by reaction with R^1R^2NH , where R^1 and R^2 each independently represent an optionally substituted alkyl, aryl, alkaryl or aralkyl group or may form a heterocyclic 30 ring together with the N-atom to which they are bound.

7. Process for the preparation of a ligand of formula 1, in which a diol having the formula $HO-C_n-OH$ with n as defined above, is reacted with PCl_3 followed by reaction with R^1R^2NH , wherein R^1 and R^2 each

independently represent an optionally substituted alkyl, aryl alkaryl or aralkyl group or may form a heterocyclic ring together with the N-atom to which they are bound.

8. Process for the asymmetric (transfer) hydrogenation of an olefinically unsaturated compound, ketone, imine or oxime derivate in the presence of a hydrogen donor and of a catalyst, wherein a catalyst represented by the formula $ML_aX_bS_c$ is used, wherein M is a transition metal, to be chosen from rhodium, iridium and ruthenium, and X is a counter ion and S is a ligand, a ranges from 0.5 to 3 and b and c, each independently, range from 0 to 2, characterized in that L is a chiral ligand of formula (I),



15 where C_n together with the two O-atoms and the P-atom forms a substituted or non-substituted ring with 2-4 C-atoms; and R^1 and R^2 each independently stand for H, an optionally substituted alkyl, aryl, alkaryl or aralkyl group or may form a heterocyclic ring together with the N-atom to which they are bound.

9. Process according to claim 8 wherein an olefinically unsaturated compound, a ketone or an imine is subjected to an asymmetric (transfer) hydrogenation.

10. Process according to claim 9 where C_n stands for a chiral C4 chain that substantially has one particular configuration.

11. Process according to claim 10, where C_n together with the two O-atoms and the P-atom forms a ring with 4 C-atoms which 2 by 2 form part of an aryl group or a naphthyl group.

12. Process according to any one of claims 8-11 in which the asymmetric (transfer) hydrogenation is carried out in the presence of a non-protic solvent.

30 13. Process according to any one of claims 8-11 in which the asymmetric (transfer) hydrogenation is carried out in the presence of an ionic liquid.

14. Process according to any one of claims 8-13 in which the hydrogen donor is chosen from the group of hydrogen, isopropanol and a mixture of formic acid and triethylamine.

15. Process according to any one of claims 8-14 in which the asymmetric (transfer) hydrogenation is carried out at a pressure of between 0.1 and 10 MPa.
16. Process according to any one of claims 8-15 in which use is made of an 5 olefin, ketone or imine that contains a chiral centre elsewhere in the molecule.
17. Process according to any one of claims 8-16 in which the catalyst is prepared in situ.
18. Process according to any one of claims 8-17, where the substrate and/or 10 the product forms a slurry with the solvent.